Estimands in SUSTAIN 8

Efficacy and safety of semaglutide vs. canagliflozin as add-on to metformin in subjects with type 2 diabetes

A phase 3b trial

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Disclaimer

- Opinions are those of the presenter and are not necessarily the views of Novo Nordisk

Primary Objective in SUSTAIN 8

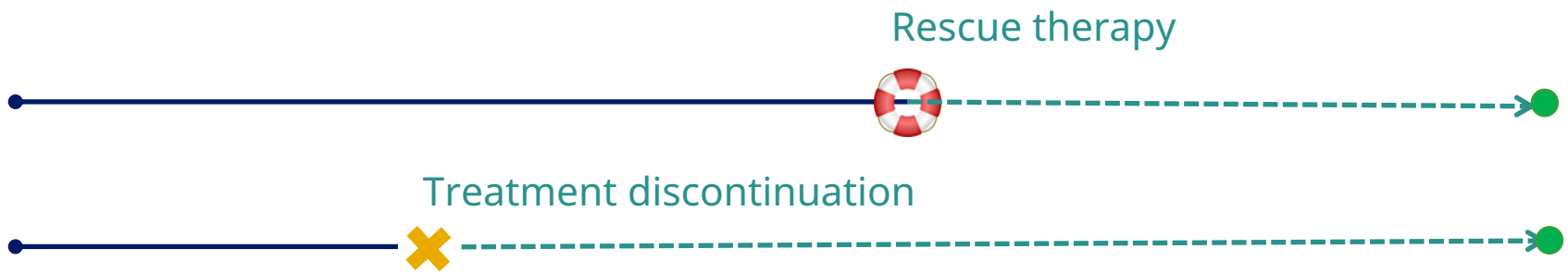
- *To compare the effect of once-weekly dosing of subcutaneous semaglutide (1.0 mg) versus once-daily dosing of oral canagliflozin (300 mg) on glycaemic control in subjects with T2D on a background treatment of metformin.*

  - To confirm non-inferiority of semaglutide s.c. (1.0 mg) vs. oral canagloflozin (300 mg) with respect to change from baseline to week 52 in HbA_{1c} (%-point) using a non-inferiority margin of 0.3%-point
  - To confirm superiority of semaglutide s.c. (1.0 mg) vs. oral canagloflozin (300 mg) with respect to change from baseline to week 52 in HbA_{1c} (%-point)

Primary Estimand in SUSTAIN 8

- Two intercurrent events (ICEs) identified
  - Treatment discontinuation for any reason
  - Use of rescue medication

- Both ICEs handled by the hypothetical strategy



Primary estimand in SUSTAIN 8

The difference between means in

change from baseline HbA1c after 52 weeks,

in patients with Type 2 diabetes,

treated with semaglutide s.c. 1.0 mg once-weekly versus oral canagliflozin 300 mg both on a background treatment of metformin,

had patients always adhered to investigational medicinal product and had rescue medication not been available.

Population-level summary measure

Endpoint

Population

Treatment Conditions

Strategies for Intercurrent Events

Rationale for primary estimand

- "…considered clinically relevant as it assesses the glycaemic benefit a person with T2D is expected to achieve if initiating and continuing treatment with semaglutide compared to initiating and continuing treatment with canagliflozin both without the potential effect of rescue medication… This will avoid confounding from rescue medication."
  - Avoiding this confounding especially important in a non-inferiority setting

- In line with the primary estimand in the SUSTAIN phase 3a studies

Who decided on the estimand

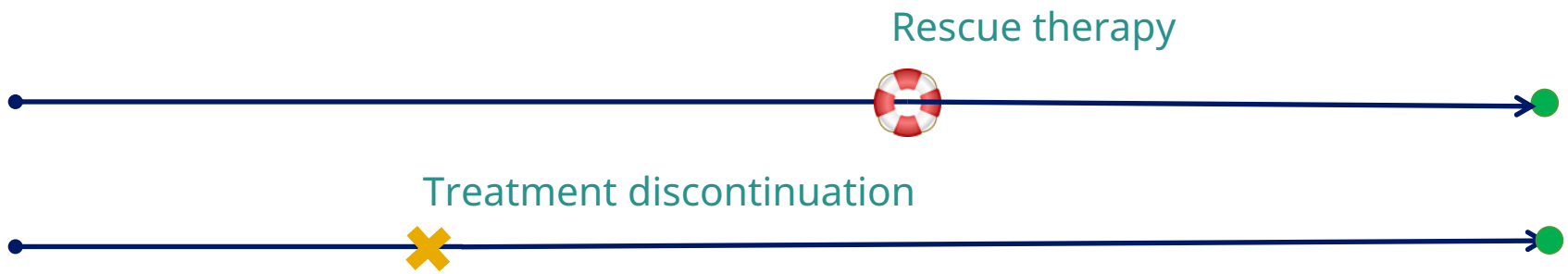
- Trial Protocol finalised end 2016 (prior to release of draft ICH E9(R1))
- Driven by the statistician in alignment with
  - Phase 3a (SUSTAIN) programme of semaglutide s.c. 0.5 mg and 1.0 mg once-weekly
  - Phase 3a programme for other diabetes projects
  - As similar as possible to current practice at the time of planning the trial

- Should be driven by the clinician with strong support from statistician

Additional Estimand in SUSTAIN 8

- Two intercurrent events (ICEs) identified
  - Treatment discontinuation for any reason
  - Use of rescue medication

- Both ICEs handled by the treatment policy strategy



Additional Estimand in SUSTAIN 8

The difference between means in

change from baseline HbA1c after 52 weeks,

in patients with Type 2 diabetes,

treated with semaglutide s.c. 1.0 mg once-weekly versus oral canagliflozin 300 mg both on a background treatment of metformin, irrespectively of adherence to investigational medicinal product and with use of rescue medication as required

Population-level summary measure

Endpoint

Population

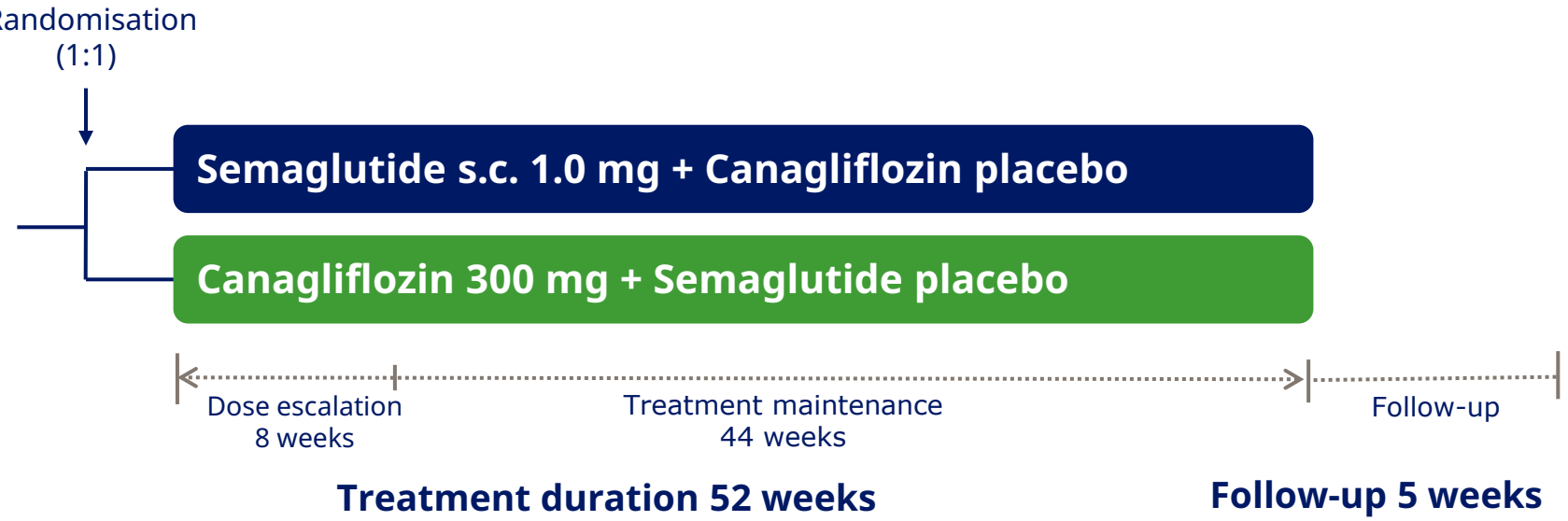
Treatment Conditions

Strategies for Intercurrent Events

Trial Design

784 subjects with T2D

- Age ≥18 years
- HbA_{1c} 7.0–10.5%
- Stable dose of metformin
- eGFR ≥ 60 mL/min/1.73 m^2



Trial information

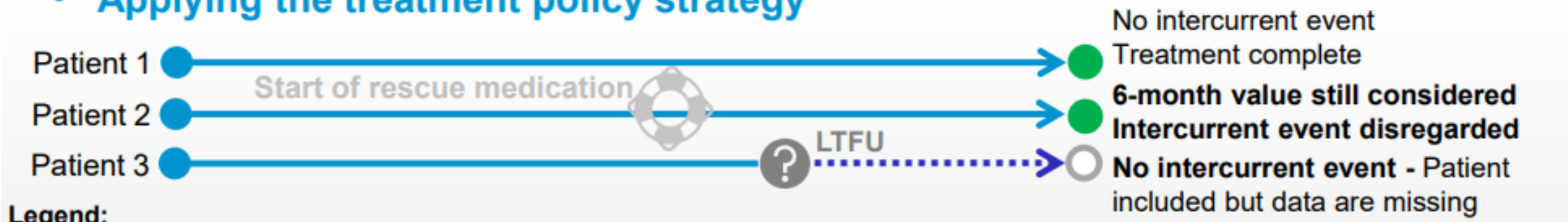
- Randomised, double-blind, double dummy, active-comparator, multicentre, multinational, two-arm, parallel group trial
- Semaglutide dose escalation from 0.25 mg and doubled every 4 weeks until maintenance dose was achieved
- Canagliflozin dose escalation from 100 mg to 300 mg after 8 weeks

eGFR, estimated glomerular filtration rate; HbA_{1c}: glycosylated haemoglobin; T2D: type 2 diabetes

Retention and Collection of Data

- **Applying a hypothetical strategy**

- **Applying the treatment policy strategy**



Legend:

- 6-month value has been collected
- 6-month value has not been collected, data are missing
- LTFU - Patient lost to follow-up
- Intercurrent event - in grey when disregarded
- Part of patient time course considered
- Part of patient time course not observed and needs to be imputed/predicted

Source: : E9(R1) EWG Step 4 Training Material, [E9(R1) Training Material - PDF_0.pdf (ich.org)]

Retention and Collection of Data are Key

- Follow-up on all randomised patients required to enable valid estimation of the additional estimand, but not for the primary
- Regulators generally prefer an estimand where all intercurrent events are handled by the treatment policy strategy
- Require full support from investigators, site staff, sponsor’s clinical operations staff

Questions?